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Circulating ghrelin levels in patients with gastric cancer: a systematic review and meta-analysis

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Background: Ghrelin plays a critical role in regulating energy metabolism and homeostasis. The association between circulating ghrelin levels and gastric cancer has not been systematically analyzed.

Objective: This work explored the association between circulating ghrelin levels and gastric cancer.

Methods: The literature search for relevant articles published until November 2022 was performed using PubMed, Cochrane Library, EMBASE, and Web of Science with the keywords "ghrelin" and "gastric cancer". Standardized mean differences (SMD) with 95% confidence intervals were used to measure the effectiveness. We assessed pooled data by use of a random-effects model.

Results: Of 5,302 identified studies, nine were included (N=3,196 participants). Circulating ghrelin levels were lower in gastric cancer patients (SMD=-0.255, 95%CI: -0.528 to 0.017, P < 0.00001), but with high heterogeneity (I² = 88.8%).

Conclusion: The circulating ghrelin levels in patients with gastric cancer were lower than in controls. However, there was heterogeneity among results; therefore, studies with larger sample sizes are recommended.

KEYWORDS

meta-analysis, ghrelin, gastric cancer, oncology, hunger hormone

Introduction

GLOBOCAN 2020 estimated 9,958,133 cancer deaths and 19,292,789 cancer cases globally (1). According to statistics, gastric cancer was the fifth most common cancer, with 1.09 million new cases (5.6%), and the fourth most common cause of cancer death, with 0.76 million deaths (7.7%) globally (1).

Gastric cancer is characterized by complex genetic and environmental interactions contributing to its initiation and progression (2). Risk factors included *Helicobacter pylori* infection, advanced age, male, smoking, high salt intake, and diets low in fruit and vegetables (3–5). The most common cause of sporadic distal gastric cancer is *H. pylori* infection (3, 4). In addition, many gastrointestinal hormones are associated with gastric cancer (6–8).

Ghrelin is an endogenous orexigenic peptide hormone of 28 amino acids that binds to the growth hormone secretagogue receptor 1 α . Kojima et al. first reported this hormone (9–11). Ghrelin is secreted by the oxyntic glands of the stomach and GHSR is expressed in pituitary gland, hypothalamus, lung, kidney, liver, adipose tissue and endocrine pancreas (9, 12). The acylation of ghrelin is essential for binding and activating its receptor but most (80–90%) circulating ghrelin is non-acylated (12, 13). Ghrelin performs several physiological functions, including orexigenic effect, growth hormone secretion stimulation, insulin secretion inhibition, and anti-inflammatory activity (9, 12, 14–16). Reviews of the role of ghrelin in cancers established associations between ghrelin and tumor progression in many different tumor types (17–20). Other studies found that circulating ghrelin levels in patients with gastric cancer decreased after gastrectomy (21, 22). These findings suggest a strong link between ghrelin and gastric cancer.

We noticed that some clinical studies found patients with gastric cancer have low circulating ghrelin levels (21–23); however, other studies reached the opposite conclusions (24, 25). Therefore, the aim of our study was to explore the association between circulating ghrelin levels and gastric cancer.

Materials and methods

Date source and search strategy

We selected relevant studies published to November 1, 2022 by searching PubMed, Cochrane Library, EMBASE and Web of Science. Medical subject headings included “ghrelin” and “tumor”. We searched the following free terms in PubMed: Neoplasias, Neoplasm, Tumors, Cancer, Malignancy, Neoplasia, Malignancy, Malignant Neoplasms, Cancers, Malignant Neoplasm, Benign Neoplasm, GHRL Protein, Benign Neoplasms, Ghrelin-Obestatin Preprohormone, Ppghrelin, Ghrelin Obestatin Preprohormone, Motilin Related Peptide Precursor, Peptide Precursor, Motilin-Related, Precursor, Motilin-Related Peptide Precursor, Motilin-Related Peptide, Ghrelin Precursor, PpMTRP, Precursor, Obestatin, Appetite-Regulating Hormone,

Ghrelin, Motilin-Related Peptide, Motilin Related Peptide Appetite Regulating Hormone, and Gastric MLTRP.

Study selection and criteria

Eligible studies met the following criteria: (1) subjects were all adults; (2) studied gastric cancer; (3) subjects included both gastric cancer patients and controls; (4) original articles with ≥ 20 subjects; (5) published in English.

The excluded research met the following criteria: (1) studies on animals; (2) studies without controls; (3) studies with substantial statistical errors or unreliable designs; (4) meta-analysis, reviews, comments and letters.

Data extraction and quality assessment

All studies were reviewed by 2 independent reviewers (Wang YX and Zhang CS) and data were extracted in a standardized format. The extracted data were as follows: study information (author, country, published year, number of men, and women study population); and subject characteristics (ghrelin levels, BMI, age, ghrelin type). The ghrelin levels were converted to unified units (pg/mL) as needed.

In the case-control study, we assessed three items using the Newcastle-Ottawa Scale (NOS): A: whether the definitions of gastric cancer were adequate; B: whether the cases were representative; C: whether the control groups were from the same community; D: whether the control subjects had a history of disease; E: Whether the designs or analyses were comparable between cases and controls; F: whether ascertainment of exposure included secure records or structured interviews that were blind to case/control status; G: whether cases and controls were ascertained identically; and H: whether the cases and controls showed identical non-response rates. An asterisk is assigned to each parameter, 0 (lowest) to 8 (highest). Studies with a score ≥ 7 were considered high quality, and other studies were classified as moderate quality.

Our meta-analysis includes data presented as an abstract in a meeting (26).

Data synthesis and analysis

Comparisons of ghrelin levels between patients with gastric cancer and controls were analyzed using a random effects model, which used mean values and standard deviations. We used standard mean difference and 95% confidence intervals to analyze continuous variables. Cochran's (chi-square) test to measure heterogeneity and the I^2 statistic to determine the extent of consistency: an I^2 of over 75% indicates a high level of inconsistency, I^2 of above 50% is moderate, and I^2 of below 25% is low (27). Differences with p-values less than 0.05 were considered statistically significant. Subgroup analysis was performed according to the ghrelin type and race. Publication bias was assessed using

Egger's regression asymmetry test. Stata MP software (Version 17.0) was used for statistical analysis.

Results

The study inclusion procedure and study characteristics

The detailed steps of study screening are shown in Figure 1. We extracted 5,302 potential literatures from PubMed, Embase, Cochrane Library, and the Web of Science. After a duplication check, 1,706 studies were removed. After review of titles and abstracts, 3,524 ineligible studies were removed. After review of the full text, 63 studies were removed. A total of 9 studies were included (21–24, 26, 28–31).

Tables 1, 2 summarize the characteristics of the included studies. Pritchett et al. studied two groups in different regions in China (23). A total of 9 studies involving 10 groups and 3,196 patients were included. The studies were published from 2005 to 2022 and the sample sizes ranged from 27 to 1546. All subjects were adults. Each group was divided into those with gastric cancer and healthy controls. Three studies included subjects from Europe (21, 26, 28), and there were six from Asia (22–24, 29–31). Blood samples were taken under fasting conditions in six of these studies (21, 22, 28–31), and not stated in the remaining three studies (23, 24, 26). Blood samples were obtained from serum in one study (24) while the remaining eight were obtained from plasma. All the studies measured non-acylated ghrelin.

Overall analysis

Ghrelin levels in patients were lower than in the control groups (Figure 2). (SMD = -0.255, 95%CI: -0.528 to 0.017). However, standard mean differences showed significant heterogeneity when

analyzed using the random-effects model ($I^2 = 88.8\%$, $P < 0.00001$). Publication bias was insignificant (Figure 3; Egger's test: $P = 0.981$). Sensitivity analysis demonstrated the stability of our meta-analysis (Figure 4).

Subgroup analysis

Subgroup analysis was performed to determine the factors affecting heterogeneity. Subgroup analyses classified by blood sample (serum or plasma) or race (Asian or European) showed no significant reductions or differences in heterogeneity (Table 3). This finding suggests that more information from different regions is needed for analysis.

Discussion

Gastric cancer is a significant cause of cancer death worldwide, with a high mortality rate. Most gastric cancer is diagnosed at an advanced stage, with poor prognosis and limited treatment options (32). Gastric cancer outcomes are significantly related to the American Joint Committee on Cancer stage. The estimated adjusted 5-year survival rate after radical surgery was 41.3%, 82.9% for stage IA and stage IB, 62.8% for stage II, 17.8% for stage IIIA and stage IIIB, and 3.3% for stage IV (33). Therefore, early diagnosis is essential.

To our knowledge, the present study is the first meta-analysis to explore the association between circulating ghrelin levels and gastric cancer. Ghrelin levels were lower in gastric cancer patients than in controls. Our findings are consistent with those of Pritchett et al. (23). Ghrelin may be used as an early marker for gastric cancer screening after stratification of metabolic status including BMI and blood glucose of residents in high incidence areas of gastric cancer.

We performed subgroup analyses according to blood sample and race to examine sources of heterogeneity. There were no significant differences or reductions in heterogeneity. It should be noted that included studies were all from Europe or Asia. We attempted to obtain studies from other continents because of the limited number of studies but failed. Many other factors may influence circulating ghrelin levels.

(1) Ghrelin levels are inversely associated with BMI. Ghrelin levels are reduced in obese patients, suggesting a physiological adaptation to the positive energy balance associated with obesity (34, 35). Few studies in our meta-analysis adjusted for the association between circulating ghrelin levels and BMI, which varied among participants and influenced ghrelin levels. (2) Cancer-related cachexia causes weight loss (mainly from loss of skeletal muscle and body fat) and inflammation (36, 37). However, some studies in our meta-analysis did not separate gastric cancer patients due to cachexia (38, 39). (3) Gastric cancer patients follow different disease progressions, and few studies analyzed patients according to American Joint Committee on Cancer stage. (4) *H. pylori* is the main pathogen causing chronic active gastritis and plays a crucial role in gastric and duodenal ulcers and gastric cancer (40). *H. pylori* infection inhibits the expression of ghrelin active cells

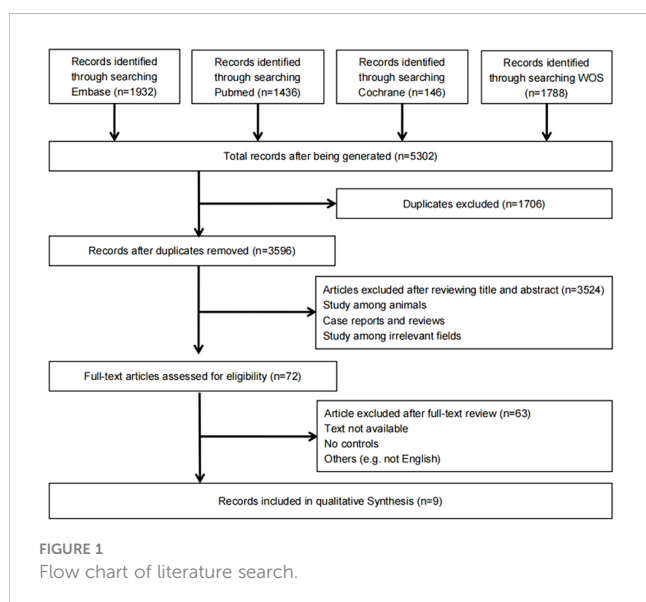


TABLE 1 Characteristics of included studies.

Author. Year	Race	Participants	Number	Blood sample	Gender (Male/Female)	Age	BMI	Ghrelin
Changzhen Zhu et al., 2020	Asian	Gastric cancer	38	Serum	29/9	Unspecified	Unspecified	22.4 ± 6.2
Qi Huang-Yue et al., 2007	Asian	Gastric cancer	58	Plasma	43/15	58.9 ± 13.3	21.8 ± 3.4	110.3 ± 92.1
Natalie R. Pritchett et al., 2020	Asian	Gastric cancer	776	Plasma	467/309	55.3 ± 8	21.7 ± 2.2	917 ± 355.6
Natalie R. Pritchett et al., 2020	Asian	Gastric cancer	249	Plasma	Unspecified	58 ± 9	24.6 ± 3.3	706 ± 259
Hai-Tao Wang et al., 2008	Asian	Gastric cancer	42	Plasma	19/23	49.5 ± 6	24.6 ± 3.3	464.6 ± 126.5
Anna Zub-Pokrowiecka et al., 2011	European	Gastric cancer	25	Plasma	14/11	49.5 ± 6	23.4 ± 2.8	191.1 ± 17.8
Krike P. et al., 2018	European	Gastric cancer	196	Plasma	Unspecified	Unspecified	Unspecified	464.2 ± 268
O Kemik et al., 2011	European	Gastric cancer	31	Plasma	14/17	46.8 ± 11.9	16.2 ± 1.5	723.7 ± 270.8
Hajime Isomoto et al., 2005	Asian	Gastric cancer	23	Plasma	11/12	60	22.1	183.2 ± 121.2
Hye-Kyung Jung et al., 2022	Asian	Gastric cancer	13	Plasma	8/5	59.2 ± 10.4	24.6 ± 2.8	631 ± 97

in the gastric mucosa, thereby reducing the level of ghrelin in the circulation. After eradication of *H. pylori* infection, ghrelin levels return to pre-infection levels (41–43). Similarly, few studies separated gastric cancer patients according to the presence or absence of *H. pylori* infection. (5) There are few related such studies, and ghrelin measurement methods are not standardized; furthermore, the normal range of ghrelin has not been determined. In many studies published in recent years, researchers have used methods to inhibit proteases followed by acidification of samples

and obtained relatively accurate results (44, 45). Unfortunately, not all studies have used such preservation techniques. As in the table, experimental data measured by different experimenters differed significantly.

The surgical options for non-early operable gastric cancer are subtotal or total gastrectomy (46). Patients undergoing gastrectomy often suffer from weight loss, which reduces their quality of life, increasing the risk of contracting other diseases and affecting long-term survival. Several studies showed that ghrelin levels decreased

TABLE 2 Characteristics of included studies.

Author. Year	Race	Participants	Number	Blood sample	Gender (Male/Female)	Age	BMI	Ghrelin
Changzhen Zhu et al., 2020	Asian	Controls	69	Serum	Unspecified	Unspecified	Unspecified	19 ± 5.8
Qi Huang-Yue et al., 2007	Asian	Controls	24	Plasma	18/6	56.7 ± 12	24.1 ± 3.8	91.4 ± 73.6
Natalie R. Pritchett et al., 2020	Asian	Controls	770	Plasma	255/515	51 ± 9	22.1 ± 2.6	1022 ± 386
Natalie R. Pritchett et al., 2020	Asian	Controls	498	Plasma	Unspecified	58 ± 9	24.8 ± 3.6	743 ± 245
Hai-Tao Wang et al., 2008	Asian	Controls	20	Plasma	8/12	40.4 ± 10.2	22.2 ± 2.2	472 ± 115.9
Anna Zub-Pokrowiecka et al., 2011	European	Controls	25	Plasma	12/13	49.3 ± 11.5	23.8 ± 2.7	302.7 ± 76.7
Krike P. et al., 2018	European	Controls	246	Plasma	Unspecified	Unspecified	Unspecified	545.9 ± 275.1
O Kemik et al., 2011	European	Controls	40	Plasma	22/18	40.4 ± 11.3	21.5 ± 2.0	1104.3 ± 201.3
Hajime Isomoto et al., 2005	Asian	Controls	39	Plasma	16/23	51	22.6	174.8 ± 125.1
Hye-Kyung Jung et al., 2022	Asian	Controls	14	Plasma	7/7	49.6 ± 5.8	22.5 ± 2.3	555.8 ± 98.4

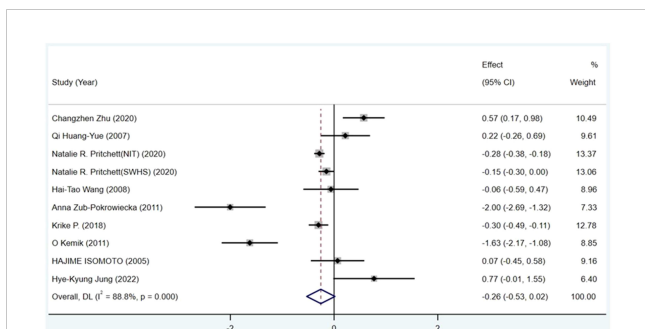


FIGURE 2 Forest plot showing the effect size of association between circulating ghrelin and gastric cancer. CI, Confidence interval. Summary estimates were analyzed using a random-effects model.

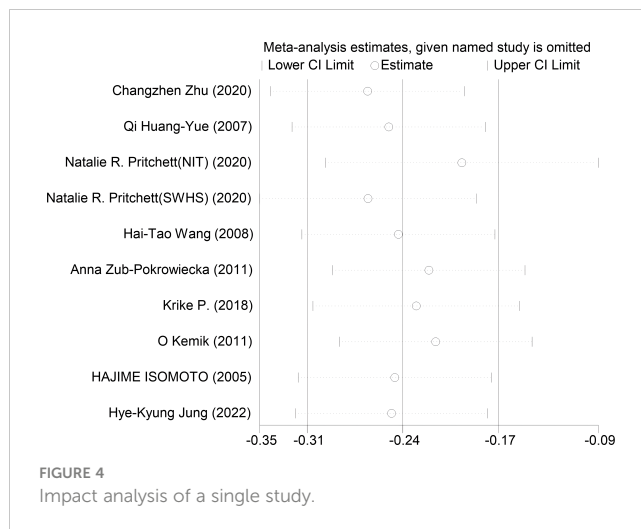


FIGURE 4 Impact analysis of a single study.

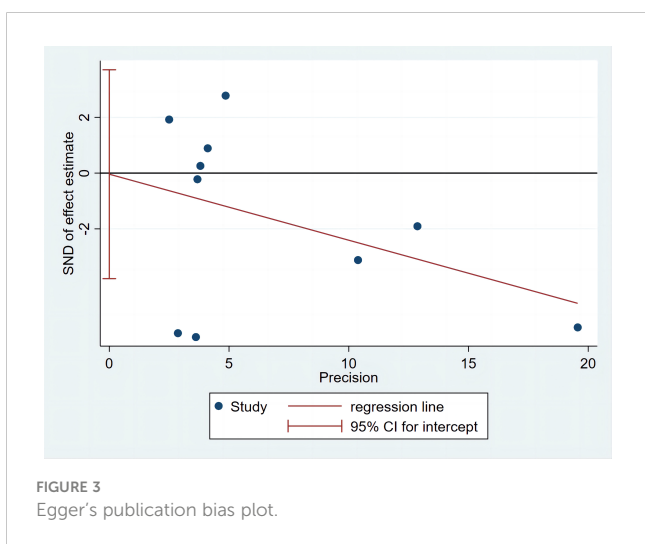


FIGURE 3 Egger's publication bias plot.

significantly after gastrectomy but recovered over time. The concentrations of ghrelin decreased to 12–29% of the preoperative levels in total gastrectomy patients and 39–71% of the preoperative levels within three days of the gastrectomy (14).

Ghrelin is the only hormone known to promote appetite; researchers noted a possible role for ghrelin in cancer-associated cachexia (47). Two studies, one in patients after gastrectomy and one in patients with advanced cancer, demonstrated the beneficial

effect of a large dose of exogenous ghrelin injection on increasing energy intake (43, 47). However, GHSR is known to express in many cancer cell types and may be upregulated in some cancers, including breast and colon cancer (48–50). Therefore, more studies are needed to demonstrate the safety of exogenous ghrelin injection.

Gastric cancer patients have different degrees of gastric atrophy, which is often accompanied by decreased ghrelin secretion (51). Therefore, the reduction of ghrelin may be a defense mechanism to limit the progression of gastric cancer. One limitation of this analysis is the small sample sizes of some studies, large-scale studies are needed to improve the accuracy of this meta-analysis. Many studies did not classify patients according to whether they had *H. pylori* infection or cachexia. Therefore, we could not make more accurate subgroup analyses based on *H. pylori* infection and cachexia. In addition, the literature search was performed using PubMed, Cochrane Library, EMBASE, and the Web of Science; Thus, language limitations may have increased the risk of publication bias.

In summary, we found that the circulating ghrelin levels were lower in patients with gastric cancer than in controls. Although the pooled results had high heterogeneity, the findings in trials with larger sample sizes agreed with our conclusion (23, 26). When ghrelin is used as an early marker for screening a large population in regions and countries with high incidence of gastric cancer, attention should be paid to factors affecting ghrelin levels,

TABLE 3 Subgroup analysis.

	Groups	Participants	Random effects (95% CI)	I ² (%)
Overall	10	3,196	-0.255 (-0.528, 0.017)	88.8
Blood sample				
Plasma	9	3089	-0.349 (-0.618, -0.079)	87.6
Serum	1	107	0.572 (0.169, 0.975)	–
Race				
Asian	7	2633	0.062 (-0.175, 0.300)	77.7
European	3	563	-1.279 (-2.448, -0.110)	94.9

CI, Confidence interval.

including the relationship between ghrelin and BMI and whether patients have *H. pylori* infection.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Author contributions

YuxW: Data curation, Formal analysis, Investigation, Methodology, Software, Writing- original draft, Writing- review & editing. CZ: Data curation, Investigation, Methodology, Software, Supervision, Writing- review & editing, Writing- original draft. QZ: Data curation, Investigation, Methodology, Software, Writing- review & editing. JY: Data curation, Methodology, Software, Writing- review & editing. YukW: Data curation, Software, Writing- review & editing. YX: Data curation, Supervision, Writing- review & editing. JD: Formal analysis, Funding acquisition, Methodology, Resources, Supervision, Writing- review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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